Penile carcinoma and HPV infection (Review)

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Abstract. Penile carcinoma is a relatively frequent health issue in the developing countries such as Africa, Asia and South America, usually affecting men aged between 50 and 70 years. It is a highly treatable disease in its early stages, but has serious physical and psychological consequences. Usually, penile carcinoma is located in the penile glans, in approximately half the cases, with the most frequent histological type being squamous cell carcinoma with its microscopic subtypes. A large number of risk factors have been reported for this disease, having a multifactorial etiology, HPV infection being one of the most important factors involved in its appearance. Out of the HPV DNA positive genital cancers HPV-16 is the most frequently found type in men, followed by HPV-18. The evolution of penile cancer includes two independent carcinogenic pathways, related or unrelated to HPV infection. There is limited data available in literature regarding HPV-related neoplasia, as well as on the efficacy of vaccination in men, with studies still ongoing.

Contents

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1. Introduction

Carcinoma of the penis is a rare neoplasm in industrialized countries, but the incidence of this malignancy is much higher in the developing countries of Africa, Asia and South America. For example, penile cancer accounts for <1% of all malignancies in men in the United States, with ~2,100 new cases and ~400 deaths annually (1). On the other hand, Brazil has the highest incidence with 2.8-6.8 per 100,000 men, with penile carcinoma being the fourth most common tumor in men (2,3).

While penile carcinoma is found more often in men aged from 50 to 70 years, it is reported that any male can be affected (4). Highly treatable in its early stages, by means of radical penile and inguinal surgery, it usually caries important physical and psychosexual morbidity for the patients who undergo such procedures. However, with the development of organ-sparing surgery, the risk of significant physical and psychological consequences is significantly lower (5).

The glans are the most common site of penile carcinoma, accounting for up to 48% of cases, followed by the prepuce (21%), glans and prepuce (9%), coronal sulcus (6%) and uncommonly the penile shaft (<2%) (6). Squamous cell carcinoma (SCC) accounts for ~95% of all penile cancer cases, followed by a wide range of other malignancies such as basal cell carcinoma, penile sarcomas, melanoma, lymphoma and metastatic disease. SCC can be classified by microscopic histologic findings into several subtypes: usual type of SCC (45-65%), papillary carcinoma (2-15%), Warty/condylomatous tumors (7-10%), basaloid carcinoma (4-10%), verrucous carcinoma (3-7%) and sarcomatoid (spindle cell) carcinoma (1-6%) (7,8).

Penile carcinoma has a multifactorial etiology, the most common risk factors being human papillomavirus (HPV) infection, phimosis and poor hygiene, as well as lack of circumcision, lichen sclerosis and inflammatory conditions (balanitis xerotica obliterans), premalignant lesions (Bowen's disease, erythroplasia Queyrat), compromised immune system, obesity, smoking, UVA phototherapy, increasing number of sexual partners and socioeconomic status.

HPV infection has been linked to penile carcinoma, the exact mechanism involved in its pathogenesis not being fully elucidated. HPV has been linked with other malignancies including cervical cancer, anal cancer and oropharyngeal cancer. More than 20% of patients with penile cancer have been tested positive for HPV infection, HPV prevalence depending on the method of sampling, processing methods and the anatomic sites or specimens sampled. The prevalence of HPV seems to be much higher in uncircumcised men compared to circumcised patients (9). HPV DNA is detected in up to 90% of cervical tumor cells and ~68% of tonsillar tumor cells (10,11).

2. HPV serotypes

Papillomaviruses are highly specific (they infect only humans), double-stranded DNA viruses that constitute the Papillomavirus genus of the Papillomaviridae family. There are more than 200 types of HPV, which can be subdivided, based on their tissue tropism, into cutaneous or mucosal categories. Human papillomaviruses (HPVs) are small, nonenveloped viruses with a circular genome that encodes eight genes and a replication cycle integrally linked to epithelial differentiation.

There are ~20 types of HPV which are known to infect the genital tract and they are classified as 'high-risk' and 'low-risk' depending on the probability to cause cancer. A study found fifteen HPV types which were classified as high risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82, with HPV-16 having the highest risk of progressing to cancer (10). Type 6 and 11 were found in benign lesions, therefore they were classified as low-risk subtypes.

In a study on human papillomavirus genotype attribution in invasive cervical cancer, the authors examined 10,575 paraffin-embedded samples and found that HPV types 16 and 18 represented 71% of all cases (11). Wiener and his colleagues, in their study on the prevalence of human papillomavirus types 16 and 18 in squamous cell carcinoma of the penis, found that these subtypes were implicated in 31% of cases, with HPV-16 being the predominant type (12).

It has been observed that HPV subtypes influence the rate of progression from infection to disease. In this light, Ingles *et al* (13) showed that 22% of HPV-11 infections developed into HPV-11 condyloma compared with only 16% of HPV-6 infections developing into specific condylomas, with a median time of 7.7 months. Furthermore, Sudenga *et al* (14) noted that only 2% of HPV-16 infections developed into PeIN, within a 2 year period.

3. HPV presence in genital lesions in men

Genitourinary HPV infections in men results in a wide spectrum of pathologies, ranging from genital warts, to penile intraepithelial neoplasia (PeIN) and penile carcinoma. Infection with oncogenic subtypes of HPV, such as HPV-16 and HPV-18, appears to be mandatory for the development of cervical cancer. Although, it appears that all cervical cancers are due to HPV infections, only a small fraction of penile carcinomas are caused by HPV. This observation has led to the assumption that penile tissue has an increased resistance to malignant transformation compared with cervical tissue. Most HPV infections do not develop into external lesions and remain asymptomatic, being immunologically cleared within 1 year (9,15). Giuliano *et al* (16), in their cohort study on human papillomavirus infection in men (HIM) found that the median time to clearance of infection was 7.5 months, with a longer clearance time (12.2 months) for HPV-16 subtype. When the infection is not cleared, it usually develops into genital warts (condyloma acuminata), resulting from the production of virus in the squamous epithelium, a benign lesion, commonly asymptomatic, but can be problematic, causing pain, itching and bleeding.

PeIN is a viral-associated preneoplastic lesion, resulting from the integration of viral genome into the DNA of the host cell, leading to oncogene overexpression and cell proliferation (17). PeIN lesions are classified as differentiated, resulting from non-viral factors such as inflammation, lichen sclerosis, phimosis, usually progressing to well-differentiated and keratinized SCC and undifferentiated, associated with HPV infections and expected to develop into basaloid and warty subtypes of SCC (18,19).

PeIN is classified into grade I, grade II and grade III, similar to the system used for cervical intraepithelial neoplasia, and it includes Erythroplasia of Queyrat (erythematous plaque on the glans and prepuce) and Bowen's disease (scaly hyperkeratotic plaque, usually on shaft of penis). Erythropasia of Queyrat has the highest risk of progressing to SCC.

In a study on the role of HPV in penile carcinoma conducted by Alemany *et al* (20) it was found that out of the 85 diagnosed precancerous lesions, 87% were positive for HPV DNA and that only 33% of penile carcinomas were HPV related. In another study up to 90% of PeIN lesions were positive for HPV DNA, with HPV-16 being the most common subtype (21). Regarding the relationship between HPV prevalence and the degree of dysplasia, Aynaud *et al* (22) found that 75% of grade I PeIN, 93% of grade II PeIN, and respectively, 100% of grade III PeIN were positive for HPV DNA.

HPV detection in penile carcinomas is very inconsistent, compared to cervical cancers, in which HPV infection is present in nearly all cases. Some studies found that HPV prevalence in penile cancers is ~46-48%, with HPV-16 and 18 representing the most common types (23,24). HPV seems to vary among the many histological SCC subtypes. The more keratinized the subtype, such as the usual and verrucous SCC, the less risk of HPV positivity. The highest HPV detection was found in the warty and basaloid subtypes of SCC. Backes *et al* (23) detected HPV in only 22.4% of the verrucous SCC cases, but it was present in 66.3% of the basaloid/warty subtypes.

The high heterogenity regarding the presence of HPV in penile cancers had some authors consider HPV presence as a prognostic marker for survival. In HPV related oropharyngeal and anal cancers studies found that HPV association may

result in improved survival (25,26). Lont *et al* (27) evaluated 176 patients regarding HPV prevalence and their survival rate and found that 29% of cases had high-risk HPV infection and was associated with a better 5-year survival rate compared with HPV-negative patients (92 vs. 78%). Another group studied 212 formalin fixed, paraffin embedded invasive penile tumor specimens of patients treated between 2001 and 2009 and found similar results, with a better 5-year disease specific survival in the high risk HPV positive group (96 vs. 86% in the HPV negative group) (28). However, some studies have failed to show similar results in terms of survival rate. Furthermore, Lopes *et al* (29), in their study evaluating p53 status as a prognostic factor, found that patients positive for p53 and HPV DNA had worse overall survival. A better understanding of HPV related carcinogenesis can improve our understanding of HPV infection as a prognostic marker.

4. HPV pathogenesis

Unlike cervical squamous cancer, in which the pathogenesis of HPV-related neoplasia is well known, the carcinogenesis of penile carcinoma is not well understood. HPV related penile cancer has been associated with warty and basaloid subtypes of SCC. Gross and Pfister (30), found HPV DNA in 100% of the warty subtypes and in 80% of the basaloid forms. On the other hand, keratinizing and verrucous subtypes had the lowest percentage of HPV DNA, 34.9% and 33.3%, respectively.

HPV affects the epithelium in two ways, either as a viral infection, in which the squamous epithelium supports the virion production, developing into low-grade lesions such as condylomas, or as a viral-associated precancerous lesion, that occurs when the viral genome is included into the DNA of the host cell, this leading to the overexpression of the oncogenes, which leads to uncontrolled cell proliferation.

Of the eight genes encoded into the viral DNA three important oncogenes are included: E5, E6 and E7. E5 oncoprotein is not necessary for malignant transformation, though its activation may contribute to carcinogenesis through manipulating viral uptake of host cells. Furthermore, E5 gene product regulates the activation of epidermal growth factor receptor (EGFR) and this will lead to a decrease of E-cadherin expression, which will furthermore favor (in a combination with other factors) the reduction of cell-to-cell adhesion. At the opposite end of the spectrum, E6 and E7 oncogenes, which are actively transcribed into the infected cells, are essential for viral-induced malignant transformation. These genes disrupt the centrosome synthesis, a vital component of cell division, with the development of multipolar cell divisions. Moreover, E6 targets p53 tumor suppressor protein, while E7 targets retinoblastoma-1 tumor suppressor protein, two negative regulators of cellular proliferation, whose inactivation leads to uncontrolled cellular proliferation (18,31,32). Some studies found that in HPV-16 induced tonsillar cancer, E6 and E7 genes are usually expressed (33,34).

Aditionally, E7 oncoprotein has been observed to have a higher affinity for retinoblastoma-1 tumor suppressor protein in high-risk HPV than in the low-risk subtypes. E7 activity on retinoblastoma-1 tumor suppressor blocks the feedback inhibition on p16ink4a, a cyclin-dependent kinase inhibitor, resulting in an increased expression of p16ink4a and its accumulation in the nucleus. A study on 53 patients with penile cancer in which 15 cases were HPV-16 induced neoplasia, found E6 and E7 transcripts in 13 patients. Immunostaining for p16ink4a showed that 12 out of the 13 patients had strong nuclear and cytoplasmic staining. This strong relationship between HPV infection and the high levels of intranuclear and intracytoplasmatic p16ink4a resulted in the use of this cyclin-dependent kinase inhibitor as an immunohistochemical marker (35,36).

5. Prevention of HPV infection in men

Preventing HPV infection is the only way to reduce HPV-related diseases, as there is no known treatment. A series of preventive measures have been proposed to minimize the risk of contracting the disease. Limiting sexual partners and condom use have been listed as methods of reducing HPV transmission (37-41).

A matter highly debatable is the presence or absence of circumcision as a preventive measure for HPV infection. A systematic review of the relationship between circumcision and human papillomavirus infection found circumcised men, compared with men who were not circumcised, had significantly reduced odds of genital HPV prevalence, with no significant association between these two groups regarding new infections, or clearance (42). It is still unclear if circumcision represents a protective measure against HPV infection. A report of three patients who underwent neonatal circumcision and later developed penile carcinoma suggested that the oncogenic potential of HPV remains despite neonatal circumcision. All three had a history of penile condyloma, and in one case oncogenic HPV had been detected in the tumor (43). Similar results were shown by other studies, with no difference in incidence between uncircumcised and circumcised men and with no protection against HPV infection (44-46). However, some studies have shown a protective effect in comparison with a control group. A randomized control trial found that high-risk HPV subtype prevalence among circumcised and uncircumcised men were 14.8 and 22.3%, respectively (47). Similarly, Tobian *et al* (48) found that the prevalence of high-risk HPV genotypes was 18.0% in the circumcised group and 27.9% in the uncircumcised group.

Although several preventive measures have been proposed, the best method of reducing HPV infection remains vaccination. The first ever vaccine approved by the FDA was Gardasil and consisted of a quadrivalent strain, covering HPV-6, 11, 16 and 18, in 2006. This was followed by the bivalent vaccine (Cervarix) in 2009 covering HPV-18 and HPV-16 in 2014, FDA approved the 9-valent version of Gardasil for HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. The majority of the published papers on HPV vaccination focus on cervical intraepithelial neoplasia and cervical cancer and less on male HPV cases. It is concerning that men have a low rate of seroconversion after natural infection and that HPV antibody seropositivity does not provide significant immunity to future infection as it does in women (49,50). However, a study that focused on the immunogenicity of the quadrivalent human papillomavirus vaccine found that it is highly efficient in men aged from 16 to 26 years, with seroconversion within 7 months, with antibodies being detected even at 36 months,

numbers comparable with those encountered in clinical trials conducted in female patients (51). In a study conducted by Giuliano *et al* (52) similar results regarding the efficacy of the quadrivalent HPV vaccine against HPV infection in male patients were found (53-61).

A systematic review regarding the efficacy, the effectiveness and the safety of vaccination against human papillomavirus in male patients concluded that vaccine effectiveness was low in individuals who are already infected with the corresponding HPV type, but was high in study groups comprising HPV-negative males, supporting a recommendation for early vaccination of boys with the goal of vaccine-induced protection before the onset of sexual activity (62).

Vaccine schedule includes a single dose, followed by a second dose 1-2 months later and afterwards a final dose 6 months later (63-68). Current recommendation regarding male vaccination from CDC Advisory Committee on Immunization Practices are as follows: routine male vaccination beginning at the age of 11 or 12 years with either the quadrivalent or 9-valent vaccine, also vaccination for males aged between 13 and 21, who have not completed a three-dose cycle. Men aged between 22 and 26 may be vaccinated as well, particularly those men who engage in sexual activity with members of the same sex and those who are immunocompromised (69-71). The European Association of Urology guidelines do not recommend vaccination as a method for reducing the risk of penile cancer.

6. Conclusions

Penile cancer is a frequent health issue in developing countries with HPV being a known risk factor for its development. High-risk subtypes of HPV have been found in up to 40% of cases, the highest detection rates are in the warty and basaloid subtypes of SCC. A better understanding of the HPV-related carcinogenesis holds the potential for future prognostic markers and a targeted treatment. There is no current treatment for HPV infection, except for the treatment of cutaneous lesions, so prevention methods and an increase of patient education are of great importance. Despite the fact that the promotion of HPV vaccination in women has led to some success regarding HPV-related cancers, the results are yet to be elucidated in the male population.

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LI, RDM, CCD, TC, DB, LF and AMAS collected, analyzed and interpreted the patient data regarding penile carcinoma and HPV infection. CCD, APS, DLDM, MS, SB and OGB made substantial contributions to the conception of the study and the interpretation of data; also, they drafted the manuscript and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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